

Amendments to the Claims

Claim 1 (previously presented): A hybrid polyketide synthase ("PKS") gene comprising a first nucleic acid portion or portions encoding at least one domain of a first type I PKS and a second nucleic acid portion or portions encoding at least one type I PKS domain which is heterologous to said first PKS.

Claim 2 (original): A hybrid PKS gene according to claim 1 wherein said first nucleic acid portion encodes at least a loading module and said second nucleic acid portion encodes at least one extension module.

Claims 3-24 (canceled)

Claim 25 (previously presented): A hybrid PKS gene according to claim 68 wherein said loading module is capable of loading a substrate to produce a starter unit different from a starter unit normally associated with said at least one extension module.

Claim 26 (canceled)

Claim 27 (currently amended): A hybrid PKS gene according to claim ~~26~~ 69, wherein said loading module is the loading module of the avermectin-producing PKS of ~~streptomyces~~ *Streptomyces avermitilis*.

Claims 28-30 (canceled)

Claim 31 (previously presented): A nucleic sequence encoding a gene according to claim 67 operably linked to a PKS type II promoter.

Claim 32 (previously presented) : A nucleic acid sequence according to claim 31, further comprising the natural activator gene for said promoter.

Claim 33 (previously presented) : A nucleic acid according to claim 31, wherein the promoter is the act I promoter of *S. coelicolor*.

Claim 34 (previously presented) : A nucleic acid according to claim 32, wherein the promoter is the act I promoter of *S. coelicolor*.

Claim 35 (previously presented) : A hybrid polyketide synthase as encoded by a gene according to claim 67.

Claim 36 (previously presented) : A vector including a gene according to claim 67.

Claim 37 (previously presented) : A transformed microorganism containing a gene according to claim 67 and able to express a polyketide synthase encoded thereby.

Claim 38 (canceled)

Claim 39 (currently amended) : A method of making a polyketide by culturing the microorganism of claim 37 wherein said microorganism is an actinomycete selected from the group consisting of: *Saccharopolyspora erythraea*, *Streptomyces coelicolor*, *Streptomyces avermitilis*, *Streptomyces griseofuscus*, *Streptomyces cinnamonensis*, *Micromonospora griseorubida*, *Streptomyces hygroscopicus*, *Streptomyces fradiae*, *Streptomyces longisporoflavus*, *Streptomyces lasaliensis*, *Streptomyces tsukubaensis*, *Streptomyces griseus*, *Streptomyces venezuelae*, *Streptomyces antibioticus*, *Streptomyces lividans*, *Streptomyces rimosus* and *Streptomyces*

albus.

Claims 40-43 (canceled)

Claim 44 (previously presented): A hybrid PKS gene according to claim 67, wherein said first nucleic acid portion encodes at least a loading module which comprises an acyltransferase and an acyl carrier protein, and said second nucleic acid portion encodes at least one extension module.

Claim 45 (canceled)

Claim 46 (canceled)

Claim 47 (previously presented): A plasmid comprising a gene according to claim 67.

Claim 48 (currently amended): A ~~transformant~~ microorganism which has been transformed so that it harbors a plasmid according to claim 47.

Claim 49 (previously presented): A transformant microorganism according to claim 48 in which said plasmid replicates autonomously.

Claim 50 (previously presented): A plasmid comprising a gene according to claim 67 which is adapted to integrate into a specific attachment site (att) of a host's chromosome.

Claim 51 (previously presented): A method of producing a transformant microorganism comprising the steps of:

- (a) producing a plasmid which comprises donor DNA which is a gene according to claim 67, and
- (b) transforming with said plasmid a microorganism having a chromosome including DNA which undergoes homologous

recombination with said plasmid to integrate said gene into the chromosome.

Claim 52 (currently amended): A method of producing a transformant microorganism comprising the step of:

(a) producing a plasmid which comprises donor DNA which encodes at least one module domain of a first Type I PKS;

(b) transforming with said plasmid an organism having a chromosome including PKS gene comprising at least one second type I PKS gene which is heterologous to said first PKS, under conditions causing integration of said donor DNA into the chromosome so as to form with a portion of said second type I PKS gene a hybrid PKS gene encoding a functional hybrid PKS which comprises at least one module domain of said first type I PKS and at least one domain of said second type I PKS.

Claim 53 (previously presented): A method according to claim 51, wherein said plasmid is adopted to integrate into a specific att site of said chromosome, said plasmid being integrated into said chromosome at a location suitable for producing said hybrid PKS gene.

Claim 54 (currently amended): A hybrid PKS gene according to claim 67, wherein said first type I PKS naturally includes a thioesterase as a chain terminating enzyme, and wherein said thioesterase in said hybrid gene includes a has been replaced with a nucleic acid sequence encoding the enzyme from the rapamycin system which, in said rapamycin system, effects connection of the polyketide chain to an amino acid chain in place of said thioesterase.

Claim 55 (previously presented): A transformed prokaryotic organism containing a gene according to claim 67 and operable to express a polyketide synthase encoded thereby.

Claim 56 (previously presented): A transformed microorganism which naturally expresses a polyketide synthase and which contains as a result of its transformation a gene according to claim 67 and is operable to express a polyketide synthase encoded thereby.

Claim 57 (currently amended): A method of making a polyketide by culturing the organism of claim 55, wherein said transformed prokaryotic organism is selected from the group consisting of: Saccharopolyspora erythraea, Streptomyces coelicolor, Streptomyces avermitilis, Streptomyces griseofuscus, Streptomyces cinnamonensis, Micromonospora griseorubida, Streptomyces hygroscopicus, Streptomyces fradiae, Streptomyces longisporoflavus, Streptomyces lasaliensis, Streptomyces tsukubaensis, Streptomyces griseus, Streptomyces venezuelae, Streptomyces antibioticus, Streptomyces lividans, Streptomyces rimosus and Streptomyces albus.

Claim 58 (currently amended): A method of making a polyketide by culturing the microorganism of claim 56, wherein said transformed prokaryotic organism is selected from the group consisting of: Saccharopolyspora erythraea, Streptomyces coelicolor, Streptomyces avermitilis, Streptomyces griseofuscus, Streptomyces cinnamonensis, Micromonospora griseorubida, Streptomyces hygroscopicus, Streptomyces fradiae, Streptomyces longisporoflavus, Streptomyces lasaliensis, Streptomyces tsukubaensis, Streptomyces griseus, Streptomyces venezuelae, Streptomyces antibioticus, Streptomyces lividans, Streptomyces rimosus and Streptomyces albus.

Claim 59 (canceled)

Claim 60 (currently amended): A method according to claim 39,

wherein said actinomycete is a ~~Streptomyces~~ selected from the group consisting of: Streptomyces coelicolor, Streptomyces avermitilis, Streptomyces griseofuscus, Streptomyces cinnamonensis, Streptomyces hygrophilus, Streptomyces fradiae, Streptomyces longisporoflavus, Streptomyces lasaliensis, Streptomyces tsukubaensis, Streptomyces griseus, Streptomyces venezuelae, Streptomyces antibioticus, Streptomyces lividans, Streptomyces rimosus and Streptomyces albus.

Claim 61 (currently amended): A hybrid polyketide synthase ("PKS") gene encoding a functional polyketide synthase comprising a plurality of modules in which a DNA portion encoding a combinatorial module has been replaced by a DNA portion encoding at ~~lease~~ least one equivalent heterologous combinatorial module, said combinatorial module being a contiguous polypeptide sequence extending from a first point in one module to a second point at the corresponding position in the next module.

Claim 62 (currently amended): A hybrid polyketide synthase ("PKS") gene encoding a functional polyketide synthase produced by

- (a) providing a first nucleic acid portion encoding a plurality of modules of a first ~~type~~ Type I PKS including a first extension module which ~~is adapted to produce~~ produces a ketide unit of a first type; and
- (b) replacing the nucleic acid encoding said first extension module with a second nucleic acid portion encoding a second extension module which is effective to produce a ketide unit of a second type, differing from said first type in at least one of the characteristics selected from the group consisting of oxidation state, stereochemistry and substitution pattern.

Claim 63 (currently amended) : A hybrid polyketide synthase (PKS) gene encoding a functional polyketide synthase comprising:

(a) a first nucleic acid portion of a first ~~type I~~ Type I PKS, said portion encoding a loading module and adjacent KS1 domain only the ketosynthase (KS) domain of the extension module which is homologous to said loading module; and

(b) a second nucleic acid portion of a second ~~type I~~ Type I PKS comprising nucleic acid encoding a partial extension module which lacks a KS domain, so that the hybrid PKS gene encodes a hybrid extension module consisting of said KS domain of the first nucleic acid portion and said partial extension module.

Claim 64 (currently amended) : A method of making a polyketide comprising:

(a) providing a transformed host microorganism selected from the group consisting of: Saccharopolyspora erythraea, Streptomyces coelicolor, Streptomyces avermitilis, Streptomyces griseofuscus, Streptomyces cinnamoneensis, Micromonospora griseorubida, Streptomyces hygroscopicus, Streptomyces fradiae, Streptomyces longisporoflavus, Streptomyces lasaliensis, Streptomyces tsukubaensis, Streptomyces griseus, Streptomyces venezuelae, Streptomyces antibioticus, Streptomyces lividans, Streptomyces rimosus and Streptomyces albus containing a gene according to claim 67 operably linked to the act I promoter of *S. coelicolor*, said host being a microorganism other than *S. coelicolor*; and

(b) culturing said transformed host microorganism to effect synthesis of said polyketide.

Claim 65 (previously presented) : The method of claim 64, wherein said host microorganism also contains the act II - orf 4 activator of *S. coelicolor*.

Claim 66 (previously presented) : The method of claim 65, wherein said transformed host microorganism is *S. erythraea*.

Claim 67 (currently amended) : A hybrid polyketide synthase (PKS) gene which encodes a functional polyketide synthase, said hybrid PKS gene comprising a first nucleic acid portion encoding multiple domains of a first Type I PKS ~~comprising at least a loading module lacking a ketosynthase (KS) activity, and at least one second nucleic acid portion encoding at least one Type I PKS domain which is heterologous to said first Type I PKS.~~

Claim 68 (currently amended) : A hybrid PKS gene according to claim 67, wherein said at least one second nucleic acid portion ~~encodes~~ encodes at least one extension module.

Claim 69 (new) : A hybrid polyketide synthase (PKS) gene according to claim 67 wherein said first nucleic acid portion encodes at least a loading module lacking a ketosynthase (KS) domain.

Claim 70 (new) : A hybrid polyketide synthase according to claim 69, wherein said loading module is selected from the group consisting of the loading modules of the rapamycin, FK506, and ascomycin -producing polyketide synthases.